PROCESS AND INTERMEDIATES FOR THE PREPARATION OF OLANZAPINE
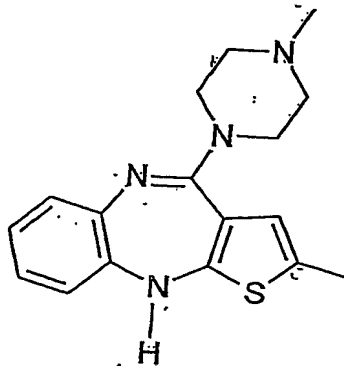
The invention belongs to the field of organic chemistry and relates to a new process and intermediates for the manufacture
5 of a compound having the following formula I:

10

i.e. 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b]-
15 [1,5]benzodiazepine (hereinafter referred to by its generic name "Olanzapine").

Olanzapine is a serotonin (5-HT$_2$) and dopamine (D$_1$/D$_2$) receptor antagonist with anticholinergic activity. It is useful in treat-
20 ing psychotic conditions such as schizophrenia, schizophreniform disorders, acute mania, states of mild anxiety and psychosis.

Heretofore, only a few processes for the manufacture of Olanzapine have become known.
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British patent GB 1,533,235 discloses a series of thieno[1,5]-benzodiazepine derivatives which are represented by the following generic formula:

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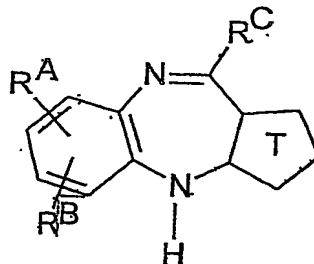
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wherein R^A and R^B represent various substituents, e.g. hydrogen, R^C represents amine substituents, e.g. 4-methylpiperazinyl, and T represents thiophene rings fused to the [1,5]-benzodiazepine ring. An example of these derivatives is 2-methyl-10H-thieno-[2,3-b][1,5]benzodiazepine. These benzodiazepine derivatives are prepared by reacting a suitable precursor with an amine HR^C so as to introduce the amine substituent R^C in the molecule.

Olanzapine and its synthesis were specifically disclosed in EP 0 454 436 A1. This application discloses two synthetic paths, which are depicted in scheme 1 below.

Both paths start with a Gewald reaction to form appropriately substituted 2-amino-thiophenes (a). This type of reaction is described in *Chem. Ber.* 1965, *98*, 3571-3577; *Chem. Ber.* 1966, *99*, 94-100. The second step involves the reaction of 2-amino-thiophene with 2-nitro-1-fluorobenzene (b), to give a 2-(2-nitro-anilino)thiophene.

According to the first reaction path, this thiophene is then (c) reduced and cyclised to a benzodiazepine-4-amine hydrochloride. Replacement of the amine group by 1-methylpiperazine (d) leads to the desired Olanzapine.

In the second reaction path, the thiophene is catalytically hydrogenated to an amino-ester (e), which is then transformed into an amino-amide (f), and this amino-amide is subsequently cyclised (g) to give Olanzapine. This second approach requires chromatographic purification in each step, because the reactions lack selectivity and because the products could not be obtained by precipitation.

Scheme 1:
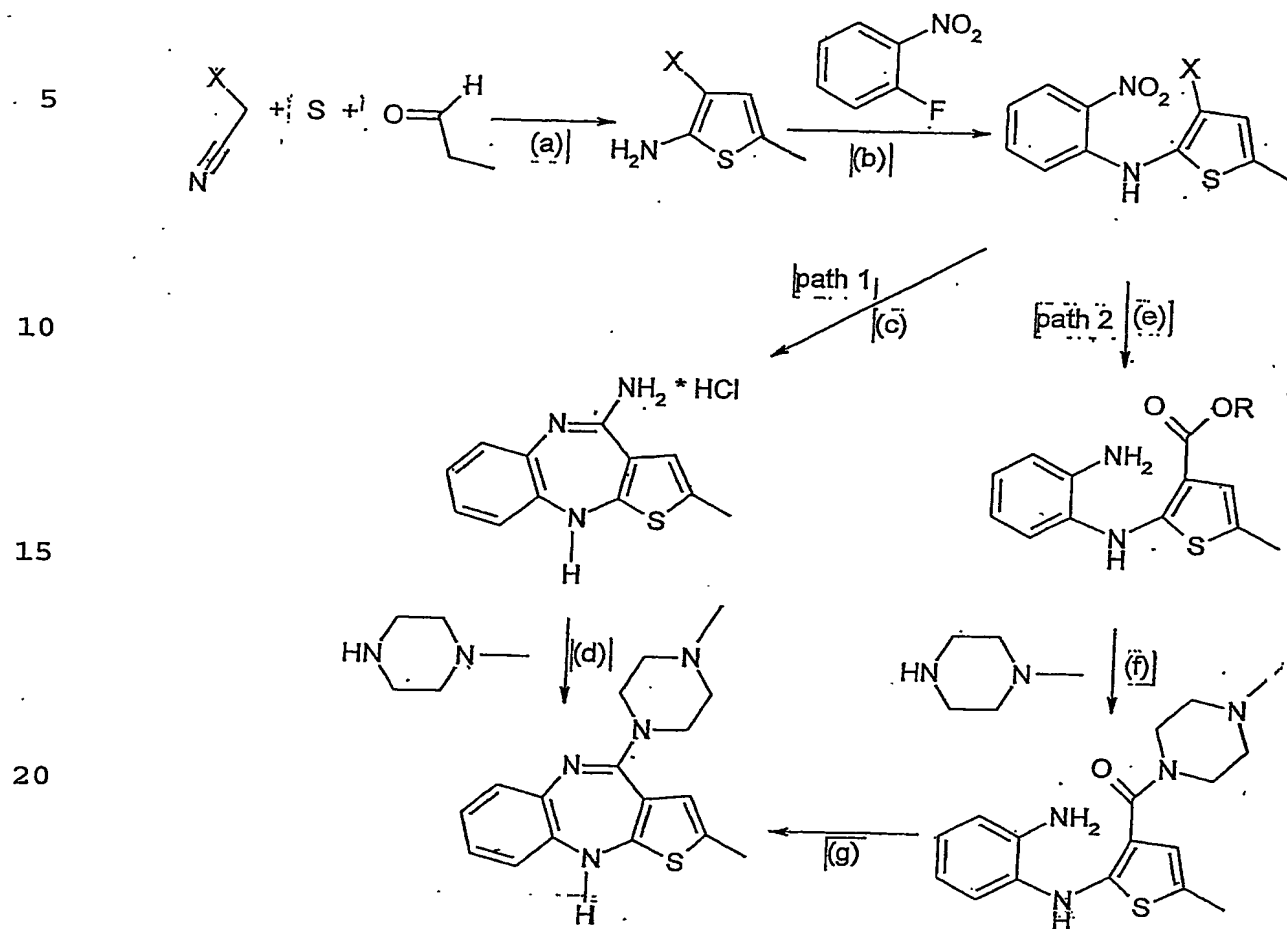
In path 1, X is CN and in path 2, X is COOR, e.g. COOC$_2$H$_5$.

The reagents used in the respective steps of the reactions were as follows: (a) Et$_3$N, DMF; (b) NaH, THF; (c) SnCl$_2$, HCl; (d) DMSO, toluene; (e) H$_2$, Pd/C, EtOH-EtOAc; (f) TiCl$_4$, anisole; (g) TiCl$_4$, anisole.

Besides the already mentioned requirement for chromatographic purification in early steps, causing high costs, low yields and substantial amounts of waste products, both paths have some further drawbacks. They provide only low yields; e.g. in the case of path 2 with X being COOC$_2$H$_5$ the yield of the first step

is only 42.5 % as is reported in *J. Heterocyclic Chem.* 36, 1999, 333-345. Other drawbacks are that expensive compounds such as Pd have to be used as well as compounds that are toxic and not acceptable from an environmental point of view, like DMF, $TiCl_4$
5 or $SnCl_2$.

Thus, there exists a need for an improved process which over- comes these drawbacks.

10 This object is surprisingly solved by the process for the manu- facture of Olanzapine according to claims 1 to 5. The invention is also directed to the compounds according to claims 6 to 9 as well as to their use according to claim 10.

15 The process according to the invention for the manufacture of Olanzapine is characterized by converting a compound of the following formula II or a salt thereof

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II
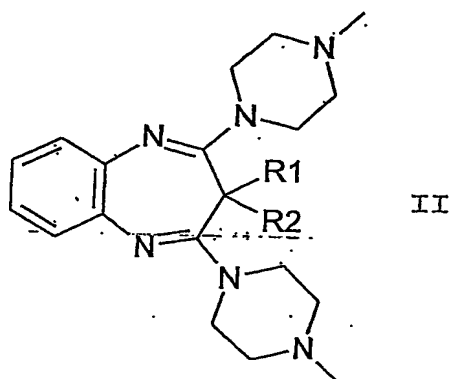
25 in which

    (i)   R1 and R2 together form $=CH-CH_2-CH_3$, or

    (ii)   R1 and R2 are both H, or

30

    (iii)   R1 is H and R2 is $-CH(R3)-CH_2-CH_3$, wherein R3 is a leaving group, that can be eliminated together with R1 to result in R1 and R2 together forming $=CH-CH_2-CH_3$, ,
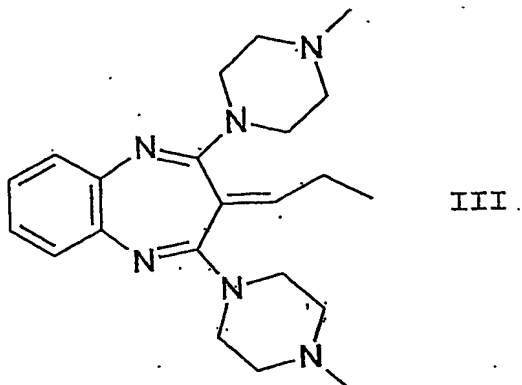
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to give Olanzapine or a salt thereof.

In the case of (i) the compound to be converted is the

propylidene-diazepine of the following formula III:
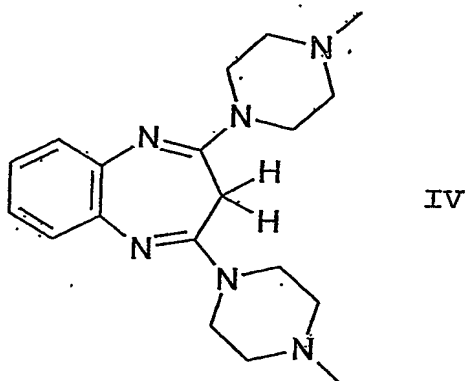
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III.

10 or a salt thereof.

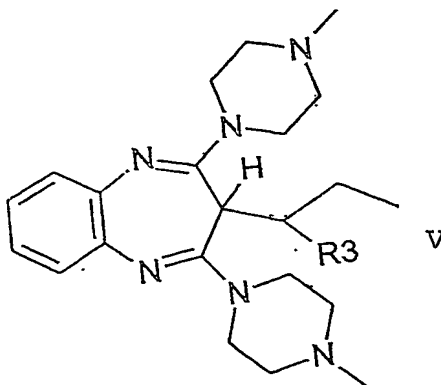In the case of (ii) the compound to be converted is the diazepine of the following formula IV:

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IV

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or a salt thereof.

In the case of (iii) the compound to be converted is the
25 diazepine-derivative bearing a leaving group R3, as is shown in the following formula V:
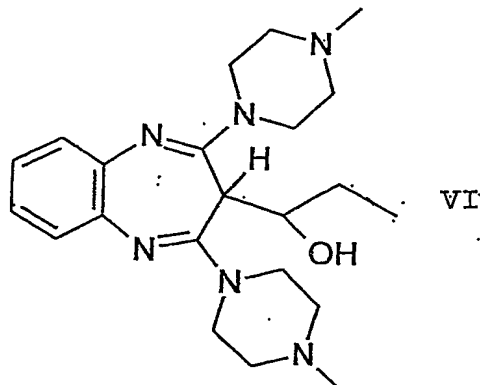
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V

35 or a salt thereof.

A preferred leaving group R3 is -OR4.

R4 can preferably be H, so that the leaving group R3 is prefer-
ably an alkohol group. In such a case the compound to be con-
verted is the diazepine-alcohol of the following formula VI:

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VI

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or a salt thereof.

R4 can also be selected from the group of acyl, sulfonyl, pre-
15 ferably trifluoroacetyl and methane sulfonyl, so that the leav-
ing group R3 is an ester group, and the compound to be converted
is the benzodiazepine-ester of the following formula VII:

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VII

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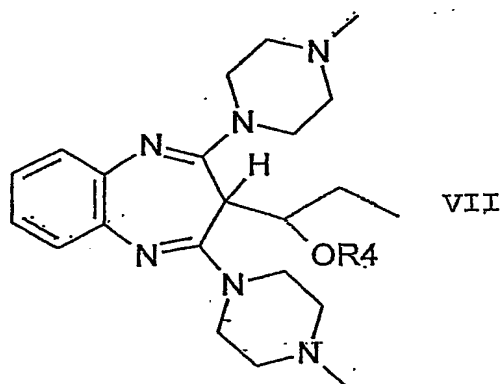
or a salt thereof with R4 being preferably selected from the
group of acyl, sulfonyl, and with R4 most preferably being
trifluoroacetyl or methane sulfonyl.
30

In a particularly preferred embodiment of the process according
to the invention, R1 and R2 together form $=CH-CH_2-CH_3$ and the
conversion is performed by reacting the compound of formula II
with a source of sulfur.
35

Particularly preferred embodiments of the process according to
this invention are depicted in scheme 2, using the preferred
precursors of the invention.

Scheme 2:
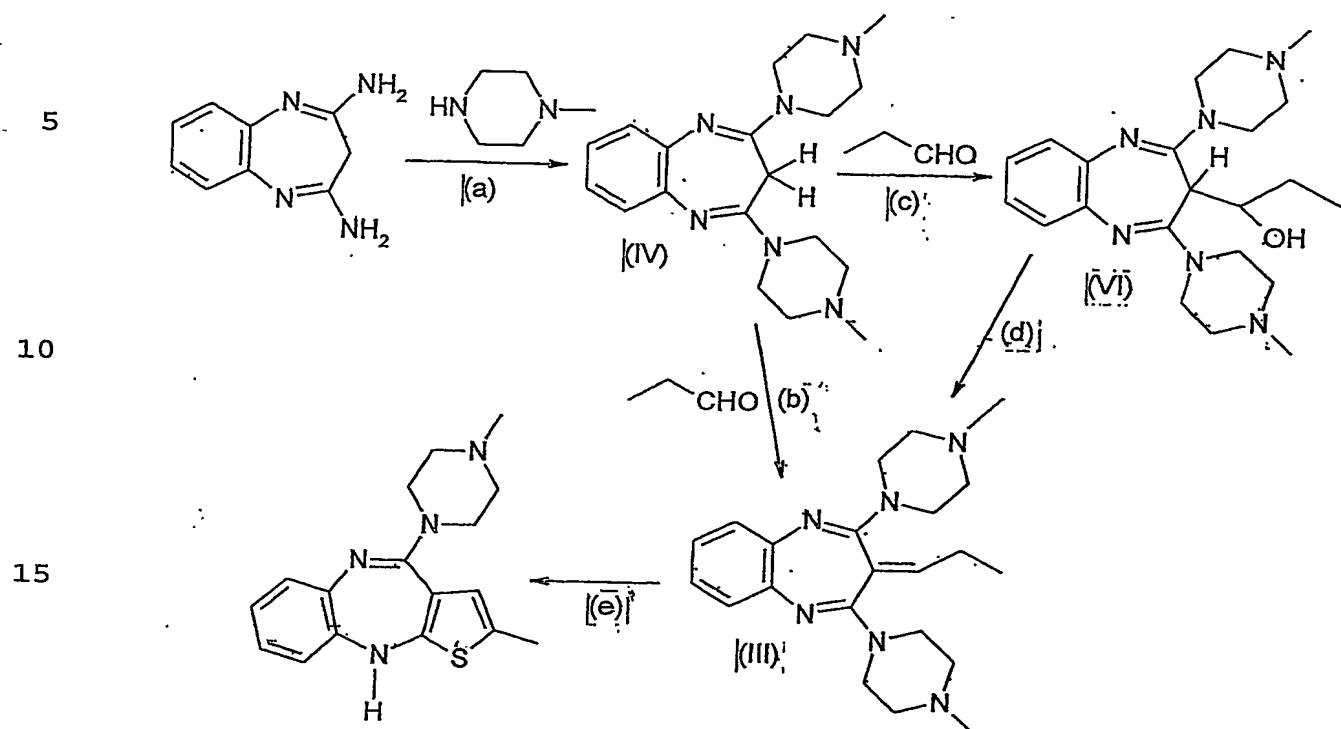
The reagents used in the respective steps are preferably as follows:

(a) Toluene, DMSO; (b) 1. LDA, THF, 2. $(CF_3CO)_2O$, NaOH; (c) LDA, THF; (d) $(CF_3CO)_2O$, NaOH, THF; (e) [S], $R^1NR^2R^2$ or AHB or AH.

Besides the advantage of the high yields in the synthesis, the use of symmetrical intermediates according to the present invention is particularly advantageous because the possibility of obtaining undesired regioisomeres is exluded.

Thus, in a first preferred aspect of the invention Olanzapine can be produced in a reaction (e) of the propylidene-benzodiazepine of formula III with a source of sulphur [S], preferably elementary sulphur or sodium polysulphide, which is usually base mediated. An appropriate base can be chosen among secondary or tertiary alkylamines of formula $R^1NR^2R^2$, in which R^1 is H or R^2, and R^2 is a C_1- to C_5-alkyl or cyclic amine such as

morpholine, piperidine, piperazine or 1-methyl-piperazine. Pre-
ferably the base is chosen from tertiary alkyl-amines and the
most preferable base is triethylamine. Acceptable solvents for
the reaction are N-methyl-imidazole, dimethyl sulfoxide (DMSO),
5 C_1- to C_5-aliphatic alcohols, alcoholamines, diols, polyols or
mixtures thereof, preferably mixtures of dimethyl sulfoxide and
alcohols. An appropriate reaction temperature range is from room
temperature to the boiling point of the reaction mixture, pre-
ferably from 50°C to 150°C and most preferably is a reaction
10 temperature of about 100°C.

The reaction can also be mediated with a salt AHB. This salt is
composed of an acid AH and an amine B. The acid AH can be chosen
among organic or anorganic acids. Preferred are organic car-
15 boxylic or sulfonic acids, such as acetic acid, trifluoroacetic
acid, benzoic acid, 4-nitrobenoic acid, 4-chlorobenzoic acid,
methanesulfonic acid, trifluoromethanesulfonic acid, benzene-
sulfonic acid or p-toluenesulfonic acid and most preferred are
p-toluenesulfonic acid or methanesulfonic acid. The amine B can
20 be chosen among secondary or tertiary aliphatic or aromatic
amines. Preferred aromatic amines are pyridine picoline, luti-
dine, quinoline, 2-methylquinoline or 1-methylimidazole and most
preferred are pyridine or quinoline. Either part of the salt AHB
can be polymer bound. Acceptable solvents for the reaction are
25 high boiling point solvents. They can be hydrocarbons, ethers,
esters, nitriles or alcohols or mixtures thereof. Preferred are
aromatic ethers, esters, or nitriles, such as anisole, di-
methoxybenzene, diphenyl ether, methyl benzoate, ethyl benzoate
and benzonitrile and most preferred is benzonitrile. An appro-
30 priate reaction temperature range is from 80°C to 220°C, prefer-
ably from 100°C to 180°C and most preferred is a reaction tem-
perature of about 140°C.

The propylidene-benzodiazepine of formula III can preferably be
35 synthesised via step (b) from the benzodiazepine of formula IV.
In a preferred embodiment the benzodiazepine IV is firstly
transformed to an alkali salt using strong bases such as alkali
amides, alkali alkyls or alkali silazanes. Preferably lithium

diisopropylamide (LDA) or butyl-lithium is used and most prefer-
ably lithium diisopropylamide is used. In an addition reaction
of the alkali salt of the benzodiazepine IV to propionaldehyde
the benzodiazepine-alcoholate of the alcohol of formula VI is
5 formed. The solvent for this reaction should be inert to strong
bases and it is in particular chosen from ethers or aromatic
hydrocarbons. Water miscible ethers are preferred, with the most
preferable solvent being THF. Usual reaction temperatures range
from -50 °C to room temperature, preferably from -30 °C to 0 °C.
10 The benzodiazepine-alcoholate is than transformed to a
benzodiazepine-ester of formula VII, in which R4 is in particu-
lar selected from the group of acyl or sulfonyl, preferably
acetyl trifluoroacetyl or methane sulfonyl, with trifluoroacetyl
being most preferred. The elimination of said ester group to
15 produce the propylidene-benzodiazepine of formula III is accom-
plished by adding of an aqueous solution of alkali hydroxide
salts such as lithium hydroxide, sodium hydroxide or potassium
hydroxide and preferably is an aqueous solution of sodium
hydroxide. When the organic solvent is immiscible with water,
20 the reaction can be catalysed with quarternary ammonium salts,
such as tetraalkylammonium chlorides, bromides, fluorides,
hydroxides or cyanides, wherein "alkyl" represents groups having
1 to 8 carbon atoms. Preferably the reaction is catalysed with
tetrabutylammonium bromide or hydroxide and most preferably with
25 tetrabutylammonium bromide. It is most preferable that the
sequence of these reactions is conducted as a one pot reaction.

Alternatively, the propylidene-diazepine of formula III can be
prepared via step (d) starting from the benzodiazepine-alcohol
30 of formula VI. The procedure is similar to the second part of
step (b). The benzodiazepine-alcohol is first transformed to a
diazepine-ester of formula VII, in which R4 is in particular
selected from the group of acyl or sulfonyl, preferably acetyl,
trifluoroacetyl or methane sulfonyl, with trifluoroacetyl being
35 most preferred. The elimination of the ester group to produce
the propylidene-benzodiazepine of formula III is preferably
carried out in a one or two phase solvent system. The organic
solvent can be chosen from ethers, halogenated hydrocarbons or

aromatic or aliphatic hydrocarbons and is preferably chosen from tetrahydrofuran, dichloromethane or toluene, with the most preferable solvent being tetrahydrofuran. The second solvent can be an aqueous solution of alkali hydroxide salts such as lithium
5 hydroxide, sodium hydroxide, or potassium hydroxide and preferably is an aqueous solution of sodium hydroxide. In case of a two phase solvent system, the reaction can be catalysed with quarternary ammonium salts such as tetraalkylammonium chlorides, bromides, fluorides, hydroxides or cyanides, wherein "alkyl"
10 represents groups having 1 to 8 carbon atoms. Preferably the reaction is catalysed with tetrabutylammonium bromide or hydroxide and most preferably with tetrabutylammonium bromide. It is most preferable that esterification and subsequent elimination of the resulting ester group are conducted as a one pot reac-
15 tion.

The benzodiazepine-alcohol of formula VI is preferably obtained via step (c) in an addition reaction of an alkali salt of the benzodiazepine of formula IV to propionaldehyde. The alkali salt
20 can be prepared using strong bases such as alkali amides, alkali alkyls or alkali silazanes. Preferably lithium diisopropylamide (LDA) or butyl-lithium is used and most preferably lithium di-isopropylamide is used. Due to this possible use of strong bases the benzodiazepine-alcohol of formula VI can also be present in
25 its deprotonized form, i.e. the corresponding benzodiazepine-alcoholate is present. The solvent for this reaction should be inert to strong bases and is in particular chosen from ethers or aromatic hydrocarbons. Ethers are preferred, with the most preferable solvent being THF. Usual reaction temperatures range
30 from -50 °C to room temperature, preferably from -30 °C to 0 °C.

The benzodiazepine of formula IV can be synthesised by reacting 3H-[1,5]benzodiazepine-2,4-diamine (J. Chem. Soc., Chem. Commun. 1973, 367-368) and 1-methylpiperazine. The reaction can be
35 carried out in a mixture of solvents comprising toluene and dimethyl sulfoxide. The reaction temperature may vary from 60°C to 180°C, preferably from 90°C to 150°C and is most preferably about 120°C.

The compounds according to formulae III to VII mentioned
hereinbefore or salts thereof as well as their use for the manu-
facture of Olanzapine are further objects of the invention.

5 By the term "or salts thereof" is meant that the compound can
not only be present in the form as is shown by formulae I to VII
but can also be present in the form of a salt e.g. a salt formed
of an organic or inorganic base and an acidic part of the com-
pound such as the alcohol group or a salt formed of an organic
10 or inorganic acid and a basic part of the compound such as the
amino-groups. The conversion of one of the substances claimed
into its salt or back into the form as is shown by formulae I to
VII is within the scope of the invention. This also applies,
when this conversion is performed as part of another reaction.
15

The invention is further illustrated with reference to the fol-
lowing examples.

Examples:

20

Example 1

Preparation of 2,4-bis(4-methyl-1-piperazinyl)-3H-[1,5]benzo-
diazepine (IV).

25

3H-[1,5]Benzodiazepine-2,4-diamine (32.50 g, 160 mmol, 86 %) was
added to a solution of dimethyl sulfoxide (220 ml), toluene (220
ml) and 1-methylpiperazine (165 ml). The mixture was heated for
16 h at 120 °C. After cooling the product precipitated. It was
30 filtered off and washed with isopropyl ether (80 ml) to give
40.1 g (74 %) of the title compound as off-white needles. The
second crop was obtained by adding isopropyl ether (410 ml) to
the filtrate. The mixture was allowed to stand overnight at 4
°C, the crystallised product was filtered off to give additional
35 4.25 g (8 %) of the title compound. For analytical purposes the
product was recrystallised from ethyl acetate.

M.P. 227-228 °C (ethyl acetate).

^{1}H-NMR (DMSO-d_6) δ = 2.21 (s, 6H), 2.35 (m, 8H), 3.02 (broad s, 2H), 3.54 (m, 8H), 6.88 (m, 2H), 7.01 (m, 2H).

HRMS calcd. for $C_{19}H_{28}N_6$: 340.2375 found: 340.2387.

5

Example 2

Preparation of 1-[2,4-bis(4-methyl-1-piperazinyl)-3H-[1,5]benzo-
10 diazepin-3-yl]-1-propanol (VI).

A suspension of 2,4-bis(4-methyl-1-piperazinyl)-3H-[1,5]benzo-diazepine (17.024 g, 50 mmol) in tetrahydrofuran (200 ml) under constant flow of argon was cooled to -30 °C. A solution of lith-ium diisopropylamide (LDA) (2 M, 37.5 ml, 75 mmol) was added
15 dropwise. Thus obtained dark brown suspension was allowed to warm to -5 °C, and then again cooled to -30 °C. Propionaldehyde (5.50 ml, 75 mmol) was added during 5 min. The resulting pale brown suspension was allowed to warm to 10 °C, while strongly agitated water (250 ml) was added. The solution was transferred
20 to a separating funnel, chloroform (150 ml) was added and the phases were separated. The water phase was extracted with chloroform (2 x 50 ml). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was evaporated at reduced pressure. The crude product was suspended in hexane (750 ml),
25 filtered off and washed with hexane (75 ml) to give 18.34 g (92 %) of the title compound as an off-white powder. For analytical purposes the product was recrystallised from ethyl acetate.

M.P. 163-166 °C (ethyl acetete).

30 ^{1}H-NMR (CDCl$_3$) δ = 0.69 (t, 3H), 1.25 (m, 2H), 2.24 (s, 3H), 2.30 (s, 3H), 2.44 (m, 8H), 3.04 (td, 1H), 3.33 (broad s, 1H), 3.57 (m, 8H), 4.51 (d, 1H), 6.98 (m, 2H), 7.10 (m, 1H), 7.22 (m, 1H).

HRMS calcd. for $C_{22}H_{34}N_6O$: 398.2794 found: 398.2806.

35

Example 3

Preparation of 2,4-bis(4-methyl-1-piperazinyl)-3-propylidene-3H-[1,5]benzodiazepine (III).

5

Method A

A suspension of 2,4-bis(4-methyl-1-piperazinyl)-3H-[1,5]benzo-diazepine (1.702 g, 5 mmol) in tetrahydrofuran (20 ml) under constant flow of argon was cooled to -30 °C. A solution of lith-
10 ium diisopropylamide (LDA) (2 M, 3.75 ml, 7.5 mmol) was added dropwise. Thus obtained dark brown suspension was allowed to warm to -5 °C until dissolved and then again cooled to -30 °C. Propionaldehyd (0.54 ml, 7.5 mmol) was added during 5 min. The resulting clear yellow solution was allowed to warm to -5 °C,
15 triethylamine (5.55 ml, 40 mmol) and pyridine (0.040 ml, 0.5 mmol) were added. A solution of trifluoroacetic anhydride (4.2 ml, 30 mmol) in tetrahydrofuran (6 ml) was added dropwise main-taining the temperature at -5 °C. The reaction mixture was stirred for another hour. Methanol (5 ml) and while strongly
20 agitated NaOH (1 M, 35 ml) were added dropwise. The reaction mixture was stirred for four hours while slowly warming to room temperature. The solution was made acidic at ph of 1 and extracted with dichloromethane (3 x 25 ml). The water phase was made alkalic at a pH of 10 and extracted with diethyl ether (15
25 x 25 ml). After each extraction water phase was adjusted to pH of 10. The ether phase was dried over anhydrous Na_2SO_4 and ether was evaporated at reduced pressure to give 1, 701 g (89 %) of the title compound as a yellow resin.

30 ^{1}H-NMR (CDCl$_3$) δ = 0.76 (t, 3H), 1.97 (m, 2H), 2.34 (s, 6H), 2.45 (m, 8H), 3.69 (m, 8H), 5.32 (t, 1H), 6.95 (m, 2H), 7.16 (m, 2H). HRMS calcd. for $C_{22}H_{32}N_6$: 380.2688 found: 380.2697.

Method B
35 To a suspension of 1-[2,4-bis(4-methyl-1-piperazinyl)-3H-[1,5]benzodiazepin-3-yl]-1-propanol (1.195 g, 3 mmol), triethylamine (2.50 ml, 18 mmol) and pyridine (0.024 ml, 0.3 mmol) in tetrahydrofuran (10 ml) under constant flow of argon,

at 0 °C, a solution of trifluoroacetic anhydride (1.26 ml, 9 mmol)in tetrahydrofuran (5 ml) was added dropwise. The reaction mixture was stirred for another hour at 0 °C. Methanol (5 ml) was added. The solution was allowed to warm to 10 °C, while strongly agitated NaOH (1 M, 20 ml) was added dropwise. Dichloromethane (30 ml) was added and the phases were separated. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated at reduced pressure. The crude product was suspended in isopropyl ether (8 ml) and filtered off. The filtrate was evaporated at reduced pressure to give 0.971 g (84 %) of the title compound as a yellow resin. The product obtained was characterized using ^{1}H-NMR spectroscopy and was found to be identical to the product obtained by method A.

Method C

To a suspension of 1-[2,4-bis(4-methyl-1-piperazinyl)-3H-[1,5]benzodiazepin-3-yl]-1-propanol (19.93 g, 50 mmol) and triethylamine (45 ml, 325 mmol) in dichloromethane (100 ml) under constant flow of argon, at 0 °C, a solution of trifluoroacetic anhydride (21 ml, 150 mmol) in dichloromethane (50 ml) was added dropwise. The reaction mixture was stirred for another hour at 0 °C. The solution was allowed to warm to room temperature. Methanol (66 ml) and tetrabutylammonium bromide (1.61 g, 5 mmol) were added successively. While strongly agitated NaOH (1 M, 660 ml) was added dropwise. Two phase system was agitated for two hours. The phases were separated and the water phase was extracted with dichloromethane (2 x 100 ml). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated at reduced pressure. The crude product was suspended in isopropyl ether (150 ml) and filtered off. the filtrate was evaporated at reduced pressure to give 14.44 g (76 %) of the title compound as a brown resin.

The product obtained was characterised using ^{1}H-NMR sprectrosopy and was found to be identical to the product obtained by method A.

Method D

A suspension of 2,4-bis(4-methyl-1-piperazinyl)-3H-[1,5]benzo-
diazepine (45.396 g, 133.3 mmol) in tetrahydrofuran (560 ml)
under constant flow of argon was cooled to -10°C. A solution of
5 lithium diisopropylamide (LDA) (2M, 100 ml, 200 mmol) was added
over a period of 20 min, maintaining the temperature at -10°C.
The obtained deep red solution was stirred for 30 min. Propio-
naldehyde (14.6 ml, 200 mmol) was added dropwise. Triethylamine
(148 ml, 1.067 mol) and pyridine (0.54 ml, 6.7 mmol) were added
10 successively. Trifluoroacetacetic anhydride (93.1 ml, 667 mmol)
was added over a period of 50 min, maintaining the temperature
at -10°C. The reaction mixture was stirred for 1 h and allowed
to warm to -5°C. Methanol (213 ml) and while strongly agitated
NaOH (5M, 200 ml, 1.000 mol) were added maintaining the tempera-
15 ture at -5°C . The reaction mixture was allowed to warm to room
temperature and stirred over night. The solution was made acidic
with 5M HCl to a pH of 3.5. Two phases were formed and the lower
layer was extracted with 600 ml and twice with 100 ml of di-
chloromethane. The aqueous phase was treated with brine (200 ml)
20 and toluene (400 ml) and made alkaline with 5M NaOH to a pH of
10. The phases were separated and the aqueous phase was
extracted with toluene (2 X 200 ml). Combined toluene phases
were dried over anhydrous Na$_2$SO$_4$ and the solvent was evaporated
at reduced pressure to give 48.38 g (95%) of the title compound
25 as an amber resin. The product obtained was characterised using
^{1}H-NMR spectroscopy and was found to be identical to the product
obtained by method A.

Example 4

30

Preparation of Olanzapine.

A suspension of 2,4-bis(4-methyl-1-piperazinyl)-3-propylidene-
3H-[1,5]benzodiazepine (11.90 g, 31.3 mmol), sulphur (20.07 g,
35 626 mmol) and triethyl amine (4.34 ml, 31.3 mmol) in dimethyl
sulfoxide (100 ml) and 1-propanol (100 ml) was heated at 100 °C
for five days. The resulting black suspension was cooled and
filtered off and the filtrate was evaporated at reduced pressure

to obtain a viscous black oil. Dichloromethane (600 ml) and HCl
(0.2 M, 600 ml) were added and the phases were separated. The
organic phase was extracted again with HCl (0.5 M, 100 ml). The
combined water phases were made alkalic at a pH of 9 to 10. Dark
5 brown precipitate was filtered off. Dichloromethane (250 ml) was
added to the filtrate. The phases were separated and the water
phase was extracted with dichloromethane (2 x 60 ml). The
organic phase was dried over anhydrous Na_2SO_4 and the solvent was
evaporated at reduced pressure. The black oil was combined with
10 precipitate and purified by chromatography on silica gel, eluted
with ethyl acetate/triethylamine 50/1 to obtain 1.195 g (12 %)
of the title product.

Example 5

15

Preparation of Olanzapine

Method A
To a 0.118 M solution of 2,4-bis(4-methyl-1-piperazinyl)-3-pro-
20 pylidene-3H-[1,5]benzodiazepine in benzonitrile (50 ml, 5.90
mmol) quinolinium p-toluenesulfonate (3.01 g, 10 mmol) and sul-
phur (0.64 g, 20 mmol) were added. The reaction mixture was
stirred at 140°C for 13.5 h, cooled to 110°C and concentrated
(78-80°C/24-30 mbar) to an oily residue. The residue was dis-
25 solved in dichloromethane (35 ml), water (30 ml) was added and
the mixture was made acidic with 2M HCl to a pH of 0.9. The
phases were separated and the aqueous phase was extracted with
dichloromethane (3 X 30 ml). The aqueous phase was made alkaline
with 15 % NaOH to a pH of 7.4 and extracted with dichloromethane
30 (2 X 30 ml). The combined dichloromethane phases were dried over
anhydrous Na_2SO_4 and the solvent was evaporated at reduced pres-
sure to give 1.91 g of crude Olanzapine. It contained 4.1 mmol
(69.5 % yield) of Olanzapine.

35 Method B
To a 0.118 M solution of 2,4-bis(4-methyl-1-piperazinyl)-3-pro-
pylidene-3H-[1,5]benzodiazepine in benzonitrile (50 ml, 5.90
mmol) pyridinium p-toluenesulfonate (2.51 g, 10 mmol) and sul

phur (0.64 g, 20 mmol) were added. The reaction mixture was
stirred at 140°C for 13.5 h, cooled to 110°C and concentrated
(78-80°C/24-30 mbar) to an oily residue. The residue was dis-
solved in dichloromethane (35 ml), water (30 ml) was added and
5 the mixture was made acidic with 2M HCl to a pH of 0.64. The
phases were separated and the aqueous phase was extracted with
dichloromethane (2 X 30 ml). The dichloromethane phases were
reextracted with diluted HCl (2 X 30 ml). The combined aqueous
phases were made alkaline with 15 % NaOH to a pH of 7.9 and
10 extracted with dichloromethane (1 X 50 ml, 2 X 30 ml). The
organic phase was dried over anhydrous Na_2SO_4. The solvent was
evaporated at reduced pressure to give 1.534 g of crude Olan-
zapine. It contained 3.93 mmol (66.6 % yield) of Olanzapine.

15 Method C
To a 0.118 M solution of 2,4-bis(4-methyl-1-piperazinyl)-3-pro-
pylidene-3H-[1,5]benzodiazepine in benzonitrile (10 ml, 1.18
mmol) 1-methylimidazolinium p-toluenesulfonate (0.51 g, 2 mmol)
and sulphur (0.128 g, 4 mmol) were added. The reaction mixture
20 was stirred at 140°C for 10 h, then it was cooled to room tem-
perature and left over night. The reaction mixture was heated to
110°C and concentrated (78-80°C/24-30 mbar) to an oily residue.
The residue was dissolved in dichloromethane (10 ml), water (10
ml) was added and the mixture was made acidic with 2M HCl to a
25 pH of 0.9. The phases were separated and the aqueous phase was
extracted with dichloromethane (3 X 6 ml). The aqueous phase was
made alkaline with 15 % NaOH to a pH of 8.5 and extracted with
dichloromethane (6 X 6 ml). The combined dichloromethane phases
were dried over anhydrous Na_2SO_4 and the solvent was evaporated
30 at reduced pressure to give 0.313 g of crude Olanzapine. It
contained 0.64 mmol (54.2 % yield) of Olanzapine.

Method D
To a 0.118 M solution of 2,4-bis(4-methyl-1-piperazinyl)-3-pro-
35 pylidene-3H-[1,5]benzodiazepine in benzonitrile (10 ml, 1.18
mmol) p-toluenesulfonic acid monohydrate (0.380 g, 2 mmol) and
sulphur (0.128 g, 4 mmol) were added. The reaction mixture was
stirred at 140°C for 9 h, cooled to 110°C and concentrated (78-

80°C/24-30 mbar) to an oily residue. The residue was dissolved in dichloromethane (15 ml), water (10 ml) was added and the mixture was made acidic with 2M HCl to a pH of 1.0. The phases were separated and the aqueous phase was extracted with di-
5 chloromethane (2 X 10 ml). The dichloromethane phases were reextracted with diluted HCl (10 ml). The combined aqueous phases were made alkaline with 15 % NaSO to a pH of 7.9 and extracted with dichloromethane (3 X 30 ml). The organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated at reduced
10 pressure to give 0.252 g of crude Olanzapine. It contained 0.61 mmol (51.7 % yield) of Olanzapine.